Medical Staff Conference

Primary Hepatocellular Carcinoma—Recent Advances and Future Prospects

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and formerly Chair of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

CRAIG FITZ, MD:* *The topic for this Medical Staff Conference is "Primary Hepatocellular Carcinoma—Recent Advances and Future Prospects," and it will be discussed by Dr Alex Tseng. Dr Tseng attended the University of Chicago Medical School and completed his house-staff training here at the University of California, San Francisco. Following an oncology fellowship at Stanford University, Dr Tseng joined our faculty July 1983 as an Assistant Professor of Medicine in the Cancer Research Institute.*

ALEX TSENG, MD:† It is estimated that in 1985 there will be nearly 1 million new cases of cancer diagnosed in the United States.[1] Primary hepatocellular carcinoma, or hepatoma, is a relatively uncommon cancer in the United States, with fewer than 3,000 cases diagnosed each year. In contrast, hepatoma is a leading cause of cancer morbidity and mortality in large areas of Asia and Africa and may account for as much as 30% to 40% of all cancer deaths. Because hepatocellular carcinoma has unique geographic incidence rates throughout the world, it is considered to be environmental in causation, although the etiology almost certainly is multifactorial.

Hepatoma is usually an aggressive and rapidly fatal disease. Exciting developments, however, in the understanding of chemical carcinogenesis and the molecular biology of the hepatitis B virus (HBV) may provide new insights into the mechanisms of hepatic oncogenesis. With these advances, we can hope that new strategies in detecting, preventing and treating cases of hepatoma will soon be developed.

Etiology and Epidemiology

Cirrhosis

Patients with hepatocellular carcinoma have a higher incidence of cirrhosis of the liver, both micronodular and macronodular. Cirrhosis of diverse causes is associated with hepatocellular carcinoma. This includes cirrhosis associated with alcohol usage, hemochromatosis and α_1-antitrypsin deficiency. The cirrhosis of Wilson's disease apparently does not result in hepatocellular carcinoma.[2]

It has been calculated that hepatocellular carcinoma will develop in roughly 3% to 10% of patients with alcoholic or dietary cirrhosis in this country but that the rate may increase to at least 10% of all cases of macronodular cirrhosis, 20% for untreated cases of hemochromatosis with cirrhosis and as much as 40% of cases of cirrhosis caused by α_1-antitrypsin deficiency.[3]

Hepatotoxins

A major etiologic factor for the development of hepatocellular carcinoma is exposure to aflatoxins. Aflatoxins are metabolites of *Aspergillus flavus* and closely related fungi. They are very potent hepatocarcinogenic substances in virtually all animals so far tested.[4] There is a significant association between aflatoxin (AFB_1) contamination of staple foods and the high frequency of human liver cancer in many developing countries. In Nigeria and many other parts of Africa, peasants may ingest several times in excess of the maximum permissible level by the World Health Organization's standards.

In the liver cell, AFB_1 is metabolized by the microsomal mixed-function-oxidase system to generate AFB_1-2,3-epoxide, which is thought to be the main carcinogenic metabolite.[5] AFB_1-2,3-epoxide is highly reactive, is capable of tight covalent binding to DNA and RNA and may be an initiating step in carcinogenesis.

Other types of primary cancers of the liver are associated with drug exposure. These include angiosarcomas, whose cause is related to thorium oxide (Thorotrast), vinyl chloride and arsenic exposure.[6] In recent years, an apparent increase in liver cell adenomas has been associated with the long-term usage of oral contraceptives.[7]

Hepatitis B Infection

HBV infection is an underlying event preceding the occurrence of hepatocellular carcinoma in a large proportion of cases, with some estimates as high as 80%.[8] The latency period in humans is generally estimated to be about 40 years.

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
5-FU = 5-fluorouracil
HBV = hepatitis B virus
MR = magnetic resonance

In high-risk populations, the disease occurs in younger age groups and is more frequent in men. Throughout the world, most cases occur among persons who are HBV carriers. Many HBV carriers in the world were probably infected in early life by their own carrier mothers. It is estimated that 85% to 90% of perinatally infected infants have indefinite persistence of HBV.[9]

It is the survival and persistence of HBV in the population on a global scale that is responsible for a huge reservoir of carriers. Epidemiologic surveys by the Centers for Disease Control indicate that about 200,000 cases of HBV infection occur each year in the United States.[10] Between 12,000 and 20,000 people become carriers each year. At least 750,000 Americans and 200 million persons in the world are estimated to be carriers of HBV, with 80% now living in Asian countries.

A long-term follow-up study to determine the incidence of hepatoma in Taiwan was begun in 1975 by Beasley and coworkers.[11] In all, 116 cases of hepatocellular carcinoma were identified in 22,707 middle-aged men, 113 cases occurred among 3,454 carriers of the hepatitis B surface antigen and 3 cases occurred among 19,253 noncarriers. Thus, there was a 217-fold excess risk of hepatocellular carcinoma in carriers after 75,000 person-years of follow-up.

Similar epidemiologic studies have been done in the People's Republic of China, and reliable statistics are available from Shanghai.[12] Liver cancer is the foremost cause of cancer deaths between the ages of 15 and 44 years of age. Overall, it is the third most common cause of cancer mortality, after stomach and lung, and accounts for 14% of all cancer deaths.

What Is the Oncogenic Role of HBV?

Despite evidence of a strong association between primary hepatocellular carcinoma and chronic infection with hepatitis B viruses in humans, the relationship between the viral agents and neoplasia remains ambiguous. Varmus suggests three possibilities.[13] HBV may make a specific genetic contribution to oncogenesis by donating a viral oncogene or by mutating a cellular gene. HBV may act as a cofactor in tumorigenesis, such as by providing an ongoing stimulus for hepatic cell regeneration, with the possibilities of cellular mutations during subsequent replication. Finally, the presence of HBV may be merely coincident with the true carcinogens.

One approach to study the relationship between HBV and hepatocellular carcinoma is to use cloned HBV DNA as a specific probe to detect HBV DNA sequences in the liver and serum of diseased patients. The technique of transfer hybridization (Southern blot) has been used by Brechot and colleagues to determine the state of the viral DNA in the hepatocyte, either free or integrated in the host cellular DNA.[14] DNA analysis of tumors from patients with hepatocellular carcinoma has shown viral integration; to date, however, no consistent pattern of integration has been found.

Rearrangements of HBV DNA or cellular sequences (or both) in the host genome could lead to the production of hepatocytes with an abnormal phenotype (cellular transformation). A focal, clonal outgrowth of these cells could lead to an eventual hepatoma.[15] Studies characterizing this proposed sequence of events may ultimately be important in understanding the factors involved in malignant transformation. Recently, antibodies have been developed that are directed against a 28,000-dalton protein (p28) found in tissues infected with HBV. The presence of p28 in tissues infected with HBV and the appearance of specific antibodies in infectious serum specimens may correlate with hepatocellular carcinoma.[16]

Pathology

In regard to gross pathology, one of three macroscopic patterns is seen: a solitary, massive tumor; multinodular tumors, or diffuse infiltrating tumors. Figure 1 shows a multinodular tumor.

The tumor may be yellow-white or varying shades of green. Bile pigmentation is more often associated with hepatoma than with cholangiocarcinoma. Hemorrhage and necroses are particularly prominent in the unilobular form. All these tumors have a propensity for invading the hepatic veins. Histologically, cells can resemble normal hepatocytes. They

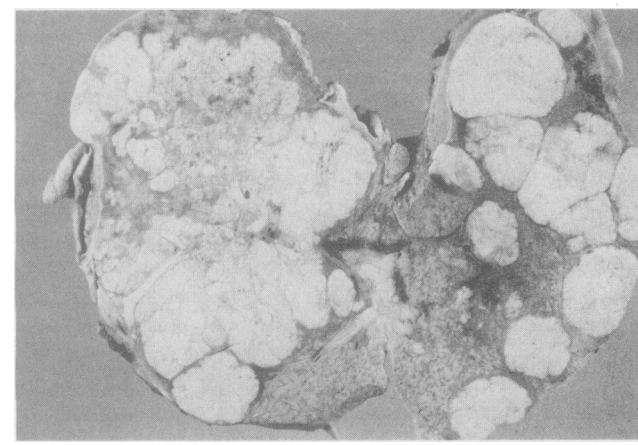

Figure 1.—Gross specimen of a multinodular hepatoma with background macronodular cirrhosis. (Courtesy of Martha Warnock, MD, Department of Pathology, University of California, San Francisco, Medical Center.)

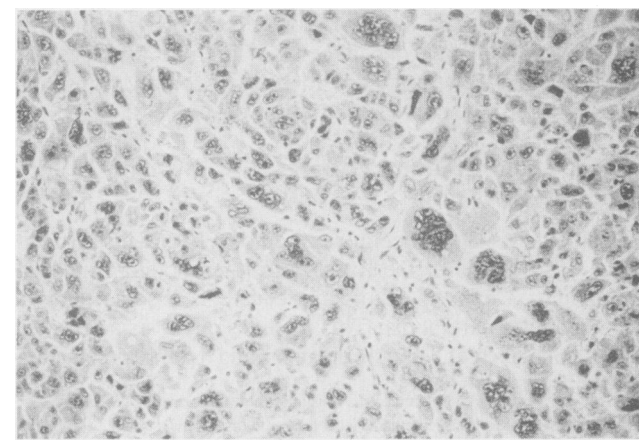

Figure 2.—Histologic picture of poorly differentiated hepatocellular carcinoma with anaplastic giant cells present (magnification × 250. Courtesy of Martha Warnock, MD, Department of Pathology, University of California, San Francisco).

can be well differentiated with cords and be separated by sinusoids. In less differentiated states, however, the cells appear as large, anaplastic giant cells (see Figure 2).

Clinical Manifestations

Signs and Symptoms

Hepatocellular carcinoma can progress rapidly and metastatic growth is commonly present, usually in the lungs, by the time a patient presents with signs and symptoms. Most patients with hepatocellular carcinoma will have right upper quadrant or epigastric pain of a chronic nature, accompanied by a right upper quadrant mass or a hard, enlarged liver.[17] This usually occurs in a patient with weight loss or increasing abdominal girth. It is not unusual for these signs and symptoms to occur in the presence of fever and jaundice.

Diagnostic Evaluation

The assessment of a patient with hepatocellular carcinoma should include methods to determine whether the patient has localized, resectable tumor, or whether the patient has extrahepatic metastases. In addition to a general physical examination, a complete blood count, liver function tests, α-fetoprotein level, chest roentgenogram and either an abdominal ultrasound study, a computed tomographic (CT) scan or a magnetic resonance (MR) imaging scan should be done.[18] Computerized, volumetric organ reconstruction of the CT or MR imaging scans may assist in quantifying tumor measurement.

MR imaging scans may also show involvement of tumor in the adjacent vascular structures. Finally, if a solitary mass involving one lobe is found, then a partial hepatectomy may be feasible, and arteriography should be done to determine the vascular supply.

General Medical Management

Lewis and Friedman have reviewed the various clinical presentations of cases of hepatoma and have described the common strategic mistakes in the care of such patients.[19] Special care must be taken with patients who have end-stage liver disease, with attention paid to hepatic synthetic function, possible precipitation of encephalopathy, associated cytopenias, coagulopathies, abnormalities in drug metabolism, fevers and paraneoplastic syndromes. From a physiologic perspective, hepatocellular cancer is a metabolically active tumor that can easily derange the fragile host environment. Physicians can do considerable harm unless they are aware of this complex milieu.

Prognostic Factors

Recognizing that hepatoma is a virulent cancer, are there prognostic factors that help discriminate between good and poor risk patients? Such discriminants would provide important information for the clinical care of an individual patient, the rational design of clinical trials and the careful interpretation of published studies.

The recognized prognostic features of importance include the state of the liver function and the patient's performance and also the histologic subtype.[20] Patients who have the fibrolamellar variant have a superior median duration of survival.[21] Pathologically, one sees deeply eosinophilic hepatocytes, intracytoplasmic hyaline globules and fibrosis arranged in a lamellar pattern. These patterns tend to be found in young women. Other factors such as α-fetoprotein levels, sex and geographic location have been analyzed as possible prognostic factors. It should be realized, however, that many of these factors are clinically interrelated and may not be independently significant.

Advances in Treatment

Surgical Treatment

If a patient presents with localized, resectable disease, a partial hepatectomy should be done. In selected cases, the five-year survival approaches 50%.[22] This compares with no five-year survivors for unresectable disease. Contraindications for partial hepatectomy include poor liver function test results, ascites, cirrhosis, extrahepatic metastases and bilobar involvement.

Scharschmidt has recently reviewed the experience of eight medical centers that collectively have carried out 819 orthotopic liver transplants since 1963.[23] In all, 155 patients have received transplants for hepatobiliary malignancy, and about 40% are still alive. Since 1983, 16 patients have had transplants in Hannover, West Germany, and in Pittsburgh, Pennsylvania, and the one-year survival probability is about 70%. Of course, longer follow-ups will be necessary before firm conclusions can be drawn.

Vaccination

Public health programs for HBV immunization are currently using vaccines that consist of subviral forms of the viral envelope that have been purified from the plasma of chronic carriers.[24-26]

In the United States, a safe and effective vaccine has been licensed, and equivalent vaccines are produced in France and the Netherlands. Vaccination trials are being conducted in Africa, Asia and Europe in the hope of controlling propagation of the chronic carrier state.

While such vaccines have established an excellent record, the expense, uncertain supply and the safety concerns associated with the plasma source have stimulated an intense interest in developing alternative sources of vaccine. Vaccines prepared by recombinant DNA and synthetic peptides methods have been shown to be immunogenic and protective in the chimpanzee model of human response. These vaccines have exciting potential as the next generation of HBV vaccines.[26]

Single-Agent Chemotherapy

For more than two decades, palliation of hepatoma patients with intravenous chemotherapy has been attempted. 5-Fluorouracil (5-FU) has been the most widely used agent. 5-FU is an antimetabolite that inhibits both DNA synthesis and RNA processing. Unfortunately, intravenous administration of a bolus of 5-FU has resulted in low partial response rates (6% to 10%).[26] There is reason to suspect, however, that prolonged intravenous infusions may be more efficacious, but no firm conclusions can be drawn at this time.[27]

Doxorubicin hydrochloride, an anthracycline drug that intercalates within DNA, is the single most effective agent for hepatoma patients. In pooling the results of six studies, doxorubicin induced an objective response in 64 of 240 patients (27%).[19] Not known is whether continuous infusions would offer greater effect. It should be noted that doxorubicin is metabolized principally by the liver and dosage reductions are

necessary in a patient with elevated bilirubin or hepatic alkaline phosphatase levels.

Combination Chemotherapy

Attempts to combine drugs to improve response rates and survival have been made. In general, combining doxorubicin or 5-FU with other drugs has not enhanced the effectiveness of either drug used individually.

Only the combination of doxorubicin plus 5-FU plus teniposide, an epidophyllotoxin, deserves further attention because an initial response rate of 44% was observed.[28]

The major criticisms of most studies of combination chemotherapy have been the relatively small number of evaluable patients and the lack of controlled trials. Therefore, larger, randomized trials testing more appropriate combinations of active drugs need to be done.

Intra-arterial Infusional Chemotherapy

It has long been recognized that liver tumors derive 90% of their nutrient blood supply from the hepatic artery. In contrast, normal hepatocytes are nourished predominantly by the portal venous system. Attempts have therefore been made to capitalize on this physiology to increase the therapeutic ratio by infusing drugs directly into the tumor via the hepatic artery. This will increase the local concentration of the antitumor agent and decrease systemic toxicity, especially if the agent is highly extracted on its first pass through the hepatic circulation.

The fluoropyrimidine drugs have a short half-life, less than ten minutes, but a high hepatic extraction ratio. For 5-FU, the hepatic extraction ratio after hepatic arterial infusion is 50% versus 30% for intravenous infusion. Even greater hepatic extraction is seen for infusions of 5-fluorodeoxyuridine (floxuridine [FUDR]), which has a 95% hepatic extraction ratio after hepatic arterial infusion versus 80% for peripheral venous infusion. Twofold to eightfold increases in hepatic drug exposure by hepatic arterial infusion are predicted for other drugs, including cisplatin, doxorubicin and dichloromethotrexate.[29]

Table 1 outlines the experience with single agents used intra-arterially. The majority of patients have received 5-FU or floxuridine. Although there have been no comparative trials of intra-arterial versus intravenous administration of fluoropyrimidine, the intra-arterial use of floxuridine appears to be superior.[30] Additionally, it appears that, given intra-arterially, doxorubicin and perhaps cisplatin may have similarly favorable pharmacokinetics and meaningful antitumor activity.[31] Although combinations of drugs given intra-arterially have also been used, it is not clear whether such combinations result in activity superior to floxuridine used alone.

The long-term administration of infusional chemotherapy once necessitated either a prolonged hospital stay or the wearing of a portable continuous infusion pumping device. Completely implantable infusion pumps have recently been developed that are highly reliable, have low morbidity and are able to administer long-term infusions into the hepatic artery.[38] However, this method of treatment should still be considered investigational because there is a spectrum of toxicities associated with intra-arterial therapy. Bleeding, occlusion, embolization and infection are recognized complications. In addition, the infusion of chemotherapy may also result in chemical hepatitis, gastritis, sclerosing cholangitis and small bowel ulceration.[39]

Last, occlusion of the hepatic artery has provided palliation to patients with hepatoma, and several studies have used intrahepatic artery infusional therapy followed by arterial ligation.[40]

Combined Modality Therapy

External radiation to the liver, while feasible, provides only limited benefit to patients with hepatoma.[41] This conclusion is based on the use of 2,000 to 3,000 rads as a single modality. However, the use of larger dose-fraction external radiation therapy may prove to be an effective means of symptom palliation without excessive risk of radiation hepatitis.

Friedman and co-workers in the Northern California Oncology Group have studied the combined use of infusional chemotherapy plus hepatic irradiation.[42] In a three-armed randomized trial, irradiation alone was compared with irradiation plus either intravenous or intrahepatic artery administration of chemotherapy. Responses were seen in 7 of 30 patients, with the greatest number in the patients receiving chemotherapy intravenously plus hepatic irradiation. The drugs were given by continuous infusion during the seven days of irradiation (300 rads daily), and toxicity was moderate (fever, anorexia, gastritis and anemia). Although response rates reached 35% to 50%, the mean duration of survival was only four months. Combined modality therapy, however, may be an effective induction regimen.

Two novel forms of internal irradiation are currently

TABLE 1.—*Intra-arterial Infusional Chemotherapy for Hepatocellular Carcinoma**

Authors	Drug	Dosage/Schedule	Patients Number	Partial Responses	Median Duration of Survival for Responders Months
Davis et al, 1974[32]	5-FU	15-30 mg/kg/d × 3 wk	9	NS	5
Pettavel and Morgenthaler, 1978[33]	5-FU	2-3 grams/d × 10 d then	11	NS	10
	Floxuridine	0.2 mg/kg/d × 12-24 wk			
Cady and Oberfield, 1974[34]	Floxuridine	0.3 mg/kg/d × 2-76 wk	18	8	20
Al-Sarraf et al, 1974[27]	Floxuridine	0.3 mg/kg/d × 3-74 wk	16	9	13
Wellwood et al, 1979[35]	Floxuridine	0.3 mg/kg/d × 8-50 wk	28	15	15
Olweny et al, 1980[36]	Doxorubicin	75 mg/m^2 q 21 d	10	4	
McIntire et al, 1976[37]	DCMTX	NS	8	0	

DCMTX = dichloromethotrexate; 5-FU = 5-fluorouracil; NS = not significant

*Modified from Lewis and Friedman.[19]

under investigation. One method uses microspheres that are coated with radioactive yttrium and are injected into the hepatic artery for local deposition of radiation. Data are fragmentary with this approach.[43] Recently workers have investigated the use of isotopic immunoglobulin using antiferritin antibody in conjunction with standard external irradiation (2,100 rads) and intravenously giving doxorubicin plus 5-FU chemotherapy.[44] This approach is currently being studied by the Radiation Therapy Oncology Group and being compared with standard chemotherapy and radiotherapy. To date, 36 patients have been enrolled. It is too early to estimate and compare the median survival between treatment groups.

Future Prospects

The foregoing studies describe a range of active therapies. It is hoped that preventing transmission of hepatitis virus infection through widespread vaccination programs in endemic areas will decrease the incidence of hepatocellular carcinoma. In addition, further advances in orthotopic liver transplantation are expected. With chemotherapy, however, there have been no complete responses reported, and its impact on overall survival is still under study. Clearly, the discovery of new, effective single agents in phase II studies is desperately needed.

Infusional chemotherapy may permit more prolonged and precise drug delivery. Greater attention to the pharmacodynamics and pharmacokinetics of these drugs may improve the therapeutic index of doxorubicin, the fluoropyrimidines and other agents. Also of interest are additional ways to use radiation therapy in conjunction with chemotherapy, by changes in fractionation schedules or by the use of intrahepatic artery administration of radiation sensitizers.[19]

Progress in monoclonal antibody research should allow even more specific targeting of radioisotopes or drug-containing liposomes to hepatoma. Hepatomas have steroid hormone receptors and can respond to progestin therapy.[45] It may be possible to shrink tumors by relatively nontoxic hormone treatment. Finally, if the nature of the oncogenic stimulus becomes apparent through basic research in carcinogenesis and viral oncology, then it may become possible to develop highly specific drug therapy to block the oncogenic stimulus or, perhaps, to induce hepatoma cells to differentiate into a benign state.

Despite the considerable problems in the care of hepatoma patients, the future for investigation has never been brighter. There are many opportunities available for those who apply modern concepts of epidemiology, molecular biology, cancer pharmacology and radiobiology to improve the care of the hepatoma patient.

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